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Title: Impact of COVID-19 on male fertility

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Abstract:

COVID-19, the clinical condition caused by the SARS-CoV-2 virus, has been associated with massive cytokine storm and damage to multiple organ systems. Although evidence for the detection of SARS-CoV-2 virus in the testis remains scarce, testicular damage and dysregulation of gonadotropins associated with inflammation has been reported. Additionally, as a result of the rapidly evolving pandemic, frequently updated medical interventions and public policies leading to delays of care can play a role in fertility. This narrative review aims to summarize the current literature on how COVID-19 may influence male fertility.

1. Introduction

Since December 2019, much of the world's news, economy, and focus has been on the Coronavirus Disease 2019, or COVID-19 virus. At this time, October 2021, there are currently 245,563,601 reported cases, 222,651,377 million people recovered, and 4,983,862 million deaths attributed to the virus [1,2]. COVID-19 is now understood to be the clinical disease caused by SARS-CoV-2. The SARS-CoV-2 virus originated in Wuhan, China. Throughout history, multiple zoonotic coronavirus pathogens have emerged and coronaviruses have been shown to adapt to different animal hosts [3]. SARS-CoV-2 shares over 96% of its genome with the bat coronavirus BatCoV RaTg13, supporting the theory that SARS-CoV-2 evolved from a bat coronavirus with an unknown intermediate host [4].

Clinically, COVID-19 presents with a persistent fever, cough, pneumonia, and loss of smell and taste. There has also been pathological evidence of massive intravascular micro-thrombotic phenomenon in multiple organs, including the lungs, heart, kidneys, brain, and testes. The interaction of the SARS-CoV-2 viral Spike protein and ACE2 on cells co-expressing ACE2 and the cellular transmembrane protease serine 2 (TMPRSS2) has been identified as the mechanism of cellular entry for the SARS-CoV-2 virus. Although not all tissues that express ACE2 are susceptible to SARS-CoV-2 infection, organ involvement has been found to be positively correlated with ACE2 expression [5]. Since the testes express ACE2 receptors, investigations into the possible influences of COVID-19 on male fertility are being actively explored [6].

The hypothalamic-pituitary-gonadal axis (HPG) endocrinologically links the brain and testis. This link is achieved through the production of gonadotropins and testosterone and the

HPG feedback loop. Precise regulation of this axis is required for optimal sex hormone production and fertility. COVID-19's effects on the hypothalamic-pituitary-gonadal axis require further evaluation, however, abnormal levels of gonadotropins have been identified in COVID-19 patients [7].

The pandemic has dramatically impacted our way of life and our medical systems and remains an ongoing and evolving public health concern. Staying current with new literature is challenging due to the high volume of studies being published. This narrative review aims to summarize the current information available investigating the relationship of COVID-19 and male infertility. We explore this relationship as it relates to hormonal regulation and the hypothalamic pituitary axis (HPG), systemic inflammation, the potential of direct testicular infection, semen parameters, interactions of medical interventions for COVID-19, and access to urologic care during the pandemic**.**

2. COVID-19 and the hypothalamic-pituitary-gonadal axis

An adequate hypothalamic-pituitary gonadal axis is crucial for maintaining normal testosterone production. Low testosterone secondary to hypergonadotropic hypogonadism, or primary hypogonadism, can be congenital as in Klinefelter Syndrome, or caused by environmental or biological disruptions to gonadal function. Low testosterone secondary to hypogonadotropic hypogonadism can lead to a secondary testicular failure. Causes for hypogonadotropic hypogonadism can be congenital, in cases such as Kallmann syndrome, or acquired secondarily from numerous causes including medication, pituitary lesions, infection, or inflammation [8]. Fertility issues associated with acquired hypogonadotropic hypogonadism can generally be corrected by fixing the underlying issue.

A selection of studies has produced data to support that COVID-19 can impact testicular hormone production. When reviewing these studies, it is important to recall that physiological stressors such as illness are associated with fluctuations in baseline hormone levels. A study by Ma et al. compared 119 reproductive aged males with SARS-CoV-2 to 273 age matched controls. They found high luteinizing hormone (LH) levels and lower testosterone to LH ratios in SARS-CoV-2 patients. The authors suggest these findings are associated with the systemic inflammation present in the evaluated patients. These abnormalities could indicate disruption in sex hormone secretion associated with COVID-19 disease [9]. Another study compared 89 COVID-19 patients to 30 patients suffering from other respiratory infections and 143 healthy controls. The COVID-19 patients were found to have significantly lower testosterone, higher LH and prolactin, and equivalent FSH when compared to both sets of controls [10]. Rastrelli et al. found that in a group of 31 patients, the 12.9% of patients who died or had severe COVID-19 exhibited lower total and free testosterone and elevated LH when compared to more moderate cases [11].

Hypothalamic pathology associated with SARS-CoV-2 infection in the brain is still being studied. SARS-CoV-2 has been shown to cross the blood brain barrier [7]. Once past the barrier, it infects ACE2 expressing cells, leading to neuroinflammation. This inflammation can disrupt normal physiologic functions such as temperature regulation and hormone balance [12–14]. Testicular pathology associated with hyperthermia has been established previously. Fevers are the body's response to systemic inflammation, and over 80% of COVID-19 patients are reported to develop a fever, which tends to be prolonged with an average duration of 10 days [15]. It has been reported that a fever of > 39°C for over three days can lead to significant reduction in semen concentration and motility [16]. While interpreting these findings, it is worth noting that

the standardized reported definitions of fever for COVID-19 patients has been poor [17].1/7/2022 10:55:00 PM

Few studies have attempted to link circulating gonadotropin levels to neuropathology in COVID -19 patients. Neuroimaging findings from a single patient study revealed a hyperintense signaling suggestive of hypothalamic lesions as well as an enlarged pituitary gland [13]. While far from conclusive, these findings suggest that hypothalamic involvement in COVID-19 patients could alter regulation of gonadotropin release leading to subsequent reduction in testosterone levels [7].

Although unlikely to lead to permanent effects on fertility, the use of glucocorticoids for the management of COVID-19 can impact fertility. Dexamethasone is one of the only medications proven to reduce mortality in COVID-19 patients and is now routinely administered [18]. A precisely balanced concentration of glucocorticoids is required to maintain gonadal function. Exogenous glucocorticoid use can disrupt the hypothalamo-pituitary-gonadal axis, which is well known to lead to temporary effects on fertility [19].

3. **Inflammation and oxidative stress**

The blood testes barrier provides privileged immunity to the testicles. However, this barrier is imperfect. The presence of systemic and local inflammation can increase this permeability and allow invasion of immune cells. SARS-CoV-2 is a cytopathic virus that creates a proinflammatory state and can lead to cell pryoptosis. Pryoptosis is an inflammatory form of programmed cell death that leads to the release of potent pro-inflammatory cytokines. Inflammatory cytokines lead to immune cell recruitment that can assist in disease clearance and further increase the production of inflammatory cytokines; in some cases, this can create a

cytokine storm, leading to uncontrolled systemic inflammation that impacts multiple organ systems [20].

Leukocytospermia often accompanies a systemic increase in IL-6, MCP-1, and TNF-α, and can be associated with systemic inflammation or viral and bacterial infections [7]. Several studies have reported an increase in inflammatory markers, including IL-6, IL-8 and TNF-α, have been identified in semen samples from patients recovering or suffering from COVID-19 compared to controls [21–23]. Additionally, CD3+, CD68+ and IgG have been identified in the seminiferous tubules of COVID-19 patients [22]. Inflammatory states, as well as states of low oxygen tension, are associated with oxidative stress and production of free radicals. Both inflammatory cytokines and oxidative stress have been found to damage cellular components of testes [24]. Oxidative stress leads to Leydig cell damage, thus disrupting capacity for testosterone production and germinal epithelial damage, which hinders spermatogenesis [25] [7]. Oxidative stress has been proposed as a potential mechanism for the testicular damage found in COVID-19 patients. However, few studies have produced data to support this claim. Moghimi et al. evaluated the production of reactive oxygen species (ROS) and glutathione disulfide (GSH) concentration in an autopsy study of six COVID-19 patients vs. six controls. They revealed a statistically significant increase in ROS and decrease of GSH in COVID-19 patients when compared to controls. These findings indicate an increase in oxidative stress and a corresponding decrease in cellular defense to oxidative stress in patients suffering from COVID-19 [26].

4. SARS-CoV-2 and potential testis infection

4.1 SARS-CoV-2 mechanism of entry

Several known single stranded RNA viruses, including other coronavirus variants like HIV, Mumps, and Zika, are known to cause orchitis and can be found in semen [27]. There is

conflicting evidence regarding the ability of SARS-CoV-2 to directly infect the testis. The mechanism of proposed entry of SARS-CoV-2 is through the binding of the SARS-CoV-2 spike protein (S-protein) viral ligand and host ACE2 receptor. The S protein is then cleaved by a serine protease co-receptor TMPRSS2, leading to membrane fusion between the virus and cell [28]. The testes express a high level of ACE2 receptors on spermatogonia, seminiferous tubules, Sertoli and Leydig cells. The endogenous function of this receptor is not yet fully understood [5]. ACE2 has a regulatory role in the male reproductive system, namely in the modulation of steroidogenesis. Additionally, ACE2 receptors are thought to play a role in fertility. This association is based on a study that observed lower levels of ACE2 in infertile men with severe spermatogenesis impairment when compared with fertile subjects [29]. Men have higher levels of TMPRSS2 expression than women. This is likely due to an androgen response element being a transcriptional promotor for TMPRSS2. It is thought that co-expression of ACE2 and TMPRSS2 are required for viral entry into cells [28].

There is discrepancy regarding the levels of ACE2 and TMPRSS2 co-expression on individual cells. Stanley et al. found that levels of ACE2 and TMPRSS2 co-expression in testicular cells occurs less than 0.05% of the time [30]. These findings are supported by a study by Pan et al. showing minimal co-expression in individuals cells [31]. Lack of co-expression would indicate minimal risk of direct infection or an alternate mechanism of entry. Levels of ACE2 mRNA and TMPRSS2 in the testis have been also examined in an autopsy study. The study examining five COVID-19 patients found that all patients had elevated levels of ACE2 and TMPRSS2 expressed in seminiferous tubules compared to controls. Immunohistochemistry showed increased expression and RT-qPCR was notable for increased mRNA levels of ACE2 and TMPRSS2. Of note, this study did not attempt to prove co-expression of ACE2 and

TMPRSS2 on an individual cell level [32]. Increased expression supports the likelihood of direct testicular invasion and damage by SARS-CoV-2. However, it remains unclear whether this increased expression of ACE2 and TMPRSS2 is actually co-expression. Additionally, increased expression of ACE2 could be secondary to underlying comorbidities such as hypertension, cancer, and smoking, rather than COVID-19 infection[33].

4.2 SARS-CoV-2 and testis histology

Several autopsy studies have attempted to identify the presence of SARS-CoV-2 virus in the testis. Only a few of these studies have successfully reported the presence of SARS-CoV-2 viral particles in the testes. These studies have small sample sizes and reports of errors in tissue sampling. Errors in sampling, including the sampling of vascular structures, has drawn questions to the validity of viral particle identification in the testis. However, the majority of studies support an association between COVID-19 and a loss of testicular architecture via changes to seminiferous tubules, Leydig cells, and germ cells. Contrary to initial theories, the data from these studies suggest that COVID-19 indirectly, rather than directly, affects testicular function [34].

Yang et al., studied the testes of 12 men who died from complications associated with COVID-19. RT-PCR identified SARS-CoV-2 RNA in one patient's testes, but electron microscopy did not confirm the presence of the SARS-CoV-2 virus in any of the 12 patients. Later discussions have suggested that this sample was fibrovascular tissue and that the viral RNA was present in sampled blood opposed to testicular tissue [35]. All 12 patients possessed a lower number of Leydig cells when compared to controls. Additionally, all COVID-19 patients showed evidence of seminiferous tubule cellular injury and a diminished population with mild

lymphocytic inflammation [36]. The authors postulated that damage to seminiferous tubules and Leydig cells may be secondary to viral membrane proteins such as the Spike protein.

In another autopsy study by Ma et al., testicles from five COVID-19 patients were studied compared to controls. All five patients were found to have degenerated germ cells sloughed off into the seminiferous tubules. In four out of five patients, almost all the germ cells lining the seminiferous tubules were lost. There was also a corresponding loss of cells expressing the germ cell marker DDX4. These findings were in direct contrast to three controls studied. The number of Sertoli cells appear consistent between control and COVID-19 patients studied [37]. SARS-CoV-2 nucleic acid was detected in the testis of two of the COVID-19 patients using RT-PCR. However, with immunohistochemistry utilizing an anti-SARS-CoV spike S1 antibody, all five COVID-19 patients stained positively. These findings suggest the ability of SARS-CoV-2 to directly infect testicular cells through spike glycoprotein binding. Transmission electron microscopy (TEM) also showed coronavirus-like particles in the interstitial compartment of the testes of all the COVID-19 patients [37].

A study by Achua et al. compared testis tissue from autopsies of six COVID-19 men to the tissue of three negative controls. Using TEM, SARS-CoV-2 viral RNA was identified in only one of the testis tissues of the COVID-19 biopsies. This tissue sample also showed interstitial macrophage and leukocyte infiltration. Three of the six COVID-19 patient biopsies showed impaired spermatogenesis, with a direct association between increased quantitative ACE-2 levels and impairment of spermatogenesis [38].

Flaifel et al. examined the testis of 10 patients who died from COVID-19. They performed RT-PCR on six of the samples and failed to identify the presence of viral RNA. They did find signs of acute damage including sloughing of spermatocytes and swelling of Sertoli cells

in all samples. The authors also reported finding microthrombi present in the testis of two of the samples, and postulated that the structural damage may be a result of hypoxic injury [23].

There have been few reports of testicular pain associated with COVID-19. One study looked at 34 men with mild to moderate COVID-19. Six men in the study complained of scrotal discomfort and tenderness. No further exam or testing such as ultrasound was completed to confirm or rule out orchitis [31]. Another study from Jordan followed 253 male patients with COVID-19 through their hospital stay and 21-day recovery period to observe for signs and symptoms of orchitis. Each patient was evaluated every two days by a urologist, but none of the patients were found to have signs or symptoms of orchitis. It was noted that most of the patients were asymptomatic or had mild-to-moderate symptoms. It remains unclear if orchitis would develop with higher viral loads, or at a later course in time [39]. In a retrospective cohort study by Liao et al., 142 patients who tested positive for COVID-19 underwent scrotal ultrasound at time of diagnosis. 22.5% of these patients were found to have increased tunica thickness and increased vascular flow consistent with orchitis, epididymitis, or epididymo-orchitis [40].

4.3 Detection of SARS-CoV-2 in semen and sperm parameters

Nearly 30 viruses have been identified in human semen [41]. Of these, the most notable are HIV, hepatitis B, herpes simplex virus (HSV), and adenoviruses. Several studies have evaluated the presence of SARS-CoV-2 in semen. Many of these studies have small sample sizes and fail to adhere to consistent semen collection parameters. With the exception of two outliers, the majority of studies suggest that detection of RNA in the semen and sexual transmission are unlikely. Additionally, the majority of data supports that semen quality, at least temporarily, is affected by COVID-19.

Most semen studies have involved recovering patients and have found that after one month, recovering patients did not have detectable levels of SARS-CoV-2 in their semen [31].The largest study by Ruan et al. consisted of 74 patients recovering from COVID-19 and 174 age matched controls. No SARS-CoV 2 RNA was detected in any of the patients, however sperm concentration count and motility were reduced [42]. Several other studies with smaller sample sizes also failed to identify SARS-CoV 2 RNA in semen samples. Hajizadeh et al. studied semen quality in patients recovering from COVID-19; comparing 84 recovering COVID-19 patients to 104 healthy controls they found impaired sperm parameters including concentration, progressive motility, and morphology in all COVID-19 patients [43]. The smaller sample sized studies reported varying reports of reduced sperm parameters, with some finding reduction, others no change, and some claiming an association with severity of COVID-19 disease [31,34,34,44–49].

Two studies have reported identifying SARS-CoV-2 RNA in the semen. One study analyzed the semen of 38 patients diagnosed with COVID-19, 15 in an acute state and 23 recovering. Six of the 38 patients were found to have SARS-COV-2 RNA in their semen; four of those six patients were in the acute stage of infection and two were in recovery. Methods of semen collection and limits of detection used for RT-PCR were not published [50]. Lastly, Gacci et al., evaluated the semen of 43 patients who had recovered from COVID-19. The presence of viral RNA was evaluated with RT-PCR at least 21 days after a negative COVID-19 test. Of the 43 patients, only one had SAR-CoV-2 RNA detected in their semen. The patient's semen sample was retested and found to be negative [21]. In studies showing viral RNA in semen, the results may be explained by sampling error or urinary or accessory sex organ involvement instead of direct testicular involvement. It is also important to recognize that even if COVID-19 is transmissible through semen, it is unlikely to provide a significant source of infection in

comparison to respiratory droplets. However, consideration should be made for those attempting to become pregnant or those donating or preserving sperm [51].

5. Effects of COVID-19 on delivering urologic care

Delayed treatment across multiple pathologies has been seen during the time of the pandemic, with people expressing fear of hospitals and avoiding medical care even in emergencies. An estimated 40.9% of surveyed US adults reported avoiding medical care, with 12% avoiding urgent or emergency care, and 31.5% avoiding routine care [52]. The delayed treatment of testicular pathology, in cases of testicular cancer or sexually transmitted infections, may impact male fertility. The concept of delayed treatment during the era of COVID-19 can be expanded to include fertility treatments.

In March of 2020 the American Society for Reproductive Medicine (ASRM) recommended the suspension of non-urgent gamete cryopreservation, new fertility treatment, and elective non urgent diagnostic procedures. Sperm banking was deemed a low priority except for patients undergoing oncological treatment [51]. At that time, concerns were raised for those suffering from non-oncological conditions that could benefit from elective fertility treatment or gamete cryopreservation. Conditions discussed included patients with hypogonadotropic hypogonadism requiring long term treatment, those with infertility thought to be associated with varicocele, and patients suffering from systemic inflammatory or autoimmune disease requiring treatments that maybe gonadotoxic [53]. At the time of authorship, restrictions for fertility services have been lifted. It is unclear what effect, if any, these temporary restrictions had on male fertility. However, being aware of previous delays in treatment may aid providers in assessing fertility concerns.

6. COVID-19 Medical Interventions

6.1 Therapies for COVID-19

Remdesivir is currently the only drug that is officially FDA approved for the treatment of COVID-19. There are seven drugs approved by the FDA under emergency use authorizations (EUA). These medications include Tocilizumab, Sotrovimab, Bamlanivimab and Etesevimab, Regen-COV (Casirivimab and Imdevimab), Baricitinib (Olumiant) and Propofol-Lipuro 1%. To our knowledge, there have been no conclusive studies to suggest that these drugs affect male fertility [54,55].

Many non-FDA approved treatments such as ribavirin, ivermectin, chloroquine and a myriad of antivirals have been used in COVID-19 patients. In rat studies, ribavirin was found to be gonadotoxic at all doses administered for a period of 105 days [56]. Some studies have suggested that prolonged use of chloroquine may impair sperm quality [57]. In general, effects of antiviral medications on male fertility require further studies [58]. Throughout 2021, ivermectin, an antiparasitic medication, gained traction across social media platforms as a potential treatment and prophylaxis for COVID-19. Claims of associations between ivermectin and male infertility also spread through social media [59]. These claims stemmed from the misinterpretation of a 2011 paper by Indonoji et. al studying sperm parameters in 37 patients with onchocerciasis treated with ivermectin [60]. Although the study identified a decrease in sperm parameters including sperm motility and count, it possessed serious limitations, including a lack of control group. Some other studies have shown ivermectin to be gonadotoxic in animal models [61], but there have been no definitive findings to suggest that ivermectin is associated with male infertility in humans. Attention should be brought to the consequences that future medications used for COVID-19 treatment may have on fertility.

6.2 COVID-19 vaccines

COVID-19 is responsible for mobilizing a collaborative effort to create a novel vaccine in record time. Prior to the COVID-19 vaccine, the fastest vaccine approved was the vaccine for the mumps virus in the 1960s, which took four years to develop. The COVID-19 vaccine was conceived, created, and approved for emergency use by the FDA in under one year. In August 2021, the Pfizer vaccine received full approval by the FDA.

Despite the pandemic ravaging the world, there is still vaccine hesitancy. Potential fertility implications after receiving a COVID-19 vaccine are a source of anxiety for many patients, as reproductive toxicity was not evaluated in clinical trials [62]. A vaccine that uses the actual virus could theoretically also directly affect the testes. However, the Pfizer and Moderna vaccines are only mRNA vaccines, which stimulate the recipient's immune system to produce the SARS-CoV-2 spike protein, and thus does not bind to receptors via the same mechanism that SARS-COV-2 virus does [63]. The Johnson & Johnson vaccine utilizes viral vector technology, combining SARS-CoV-2 spike gene with a weakened adenovirus. This leads to expression of the spike protein on cellular surfaces for immune cell interaction [64]. Although unlikely, there is a theoretical risk for expressed spike protein interaction in the testis.

A single centered prospective study out of the University of Miami investigated the effects of COVID-19 vaccination on semen parameters. A sample of 45 healthy male volunteers provided semen samples before the first vaccination dose and again, 70 days after the second dose administration. Semen samples were analyzed for the following parameters: semen volume, sperm concentration, sperm motility and total motile sperm count. No significant decreases in any of the above parameters were found [65]. There is a potential for a temporary decrease in sperm production post-vaccine, related to vaccine induced fevering. A fever can temporarily

impact sperm count, and in the Pfizer vaccine clinical trials about 16% of men experienced a fever after the second vaccine dose. However, this brief impact on sperm after vaccination is likely of much less magnitude than any potential effects of having the full clinical syndrome of COVID-19 [63].

Although there is limited data on the impact of the COVID-19 vaccines on male fertility, the Society for Male Reproduction and Urology (SMRU) and the Society for the Study of Male Reproduction (SSMR) have made two recommendations regarding vaccinations. Firstly, the COVID-19 vaccine should not be withheld from men desiring fertility who meet criteria for vaccination. Secondly, the COVID-19 vaccines should be offered to all men desiring fertility and all men not desiring fertility when they meet criteria for vaccination.

7. Limitations

It is important to note that the data that has been presented on COVID-19 and infertility has surfaced within the short time frame since the virus was recognized in 2019. Sample sizes are generally small and many clinical studies are performed at single sites, making it unwise to draw definitive conclusions from their findings. This is an evolving virus and will continue to require dynamic research to truly understand it's lasting impacts on the male reproductive tract and fertility.

8. Concluding statements

While much is left to be studied, COVID-19 does appear to impact male fertility, at least temporarily. From review of the current literature, it has become evident that COVID-19 can lead to a reduction in testosterone production and a state of temporary hypogonadism. It was originally hypothesized that since the testes are prone to direct infection by the SARS-CoV-2 virus due to their ACE2 expression, male fertility is adversely affected. Although controversy

remains, the data supports that a reduction in testosterone production is more likely associated with indirect testicular damage due to systemic or local inflammation. Additionally, with the rapidly evolving pandemic, it is important to maintain vigilance for potential interventions and delays of care that can lead to lasting effects on fertility. Moving forward, further studies are required to investigate the potential long term fertility effects of the COVID-19 disease, treatments, and vaccines.

Declaration of competing interest

The authors declare no conflicts of interest.

References

[1] Coronavirus (COVID-19), Google News. (n.d.). https://news.google.com/covid19/map?hl=en-US&gl=US&ceid=US:en (accessed April 8, 2021).

[2] COVID Live Update: 245,563,601 Cases and 4,983,862 Deaths from the Coronavirus - Worldometer, (n.d.). https://www.worldometers.info/coronavirus/ (accessed October 27, 2021).

[3] M.R. Denison, R.L. Graham, E.F. Donaldson, L.D. Eckerle, R.S. Baric, Coronaviruses, RNA Biol. 8 (2011) 270–279. https://doi.org/10.4161/rna.8.2.15013.

[4] R. Yan, Y. Zhang, Y. Li, L. Xia, Y. Guo, Q. Zhou, Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2, Science. 367 (2020) 1444–1448. https://doi.org/10.1126/science.abb2762.

[5] J. Hallak, T.A. Teixeira, F.S. Bernardes, F. Carneiro, S.A.S. Duarte, J.R. Pariz, S.C. Esteves, E. Kallas, P.H.N. Saldiva, SARS-CoV-2 and its relationship with the genitourinary tract: Implications for male reproductive health in the context of COVID-19 pandemic, Andrology. 9 (2021) 73–79. https://doi.org/10.1111/andr.12896.

[6] Y. Chen, Y. Guo, Y. Pan, Z.J. Zhao, Structure analysis of the receptor binding of 2019-nCoV, Biochem. Biophys. Res. Commun. (2020). https://doi.org/10.1016/j.bbrc.2020.02.071.

[7] K. Selvaraj, S. Ravichandran, S. Krishnan, R.K. Radhakrishnan, N. Manickam, M. Kandasamy, Testicular Atrophy and Hypothalamic Pathology in COVID-19: Possibility of the Incidence of Male Infertility and HPG Axis Abnormalities, Reprod. Sci. (2021) 1–8. https://doi.org/10.1007/s43032-020-00441-x.

[8] R. Fraietta, D.S. Zylberstejn, S.C. Esteves, Hypogonadotropic hypogonadism revisited, Clin. Sao Paulo Braz. 68 Suppl 1 (2013) 81–88. https://doi.org/10.6061/clinics/2013(sup01)09.

[9] L. Ma, W. Xie, D. Li, L. Shi, G. Ye, Y. Mao, Y. Xiong, H. Sun, F. Zheng, Z. Chen, J. Qin, J. Lyu, Y. Zhang, M. Zhang, Evaluation of sex-related hormones and semen characteristics in reproductive-aged male COVID-19 patients, J. Med. Virol. 93 (2021) 456–462. https://doi.org/10.1002/jmv.26259.

[10] Y. Pazir, T. Eroglu, A. Kose, T.B. Bulut, C. Genc, M. Kadihasanoglu, Impaired semen parameters in patients with confirmed SARS-CoV-2 infection: A prospective cohort study, Andrologia. 53 (2021) e14157. https://doi.org/10.1111/and.14157.

[11] G. Rastrelli, V. Di Stasi, F. Inglese, M. Beccaria, M. Garuti, D. Di Costanzo, F. Spreafico, G.F. Greco, G. Cervi, A. Pecoriello, A. Magini, T. Todisco, S. Cipriani, E. Maseroli, G. Corona, A. Salonia, A. Lenzi, M. Maggi, G. De Donno, L. Vignozzi, Low testosterone levels predict clinical adverse outcomes in SARS-CoV-2 pneumonia patients, Andrology. 9 (2021) 88–98. https://doi.org/10.1111/andr.12821.

[12] Y. Wu, X. Xu, Z. Chen, J. Duan, K. Hashimoto, L. Yang, C. Liu, C. Yang, Nervous system involvement after infection with COVID-19 and other coronaviruses, Brain. Behav. Immun. 87 (2020) 18–22. https://doi.org/10.1016/j.bbi.2020.03.031.

[13] E. Pascual-Goñi, J. Fortea, A. Martínez-Domeño, N. Rabella, M. Tecame, C. Gómez-Oliva, L. Querol, B. Gómez-Ansón, COVID-19-associated ophthalmoparesis and hypothalamic involvement, Neurol. Neuroimmunol. Neuroinflammation. 7 (2020). https://doi.org/10.1212/NXI.0000000000000823.

[14] A.M. Baig, A. Khaleeq, U. Ali, H. Syeda, Evidence of the COVID-19 Virus Targeting the CNS: Tissue Distribution, Host-Virus Interaction, and Proposed Neurotropic Mechanisms, ACS Chem. Neurosci. 11 (2020) 995–998. https://doi.org/10.1021/acschemneuro.0c00122.
[15] M.H. Gul, Z.M. Htun, A. Inayat, Role of fever and ambient temperature in COVID-19, Expert Rev. Respir. Med. (n.d.) 1–3. https://doi.org/10.1080/17476348.2020.1816172.
[16] A. Jung, H.-C. Schuppe, Influence of genital heat stress on semen quality in humans, Andrologia. 39 (2007) 203–215. https://doi.org/10.1111/j.1439-0272.2007.00794.x.
[17] A. Grünebaum, F.A. Chervenak, L.B. McCullough, J.W. Dudenhausen, E. Bornstein, P.A. Mackowiak, How fever is defined in COVID-19 publications: a disturbing lack of precision, J. Perinat. Med. 49 (2021) 255–261. https://doi.org/10.1515/jpm-2020-0546.
[18] Dexamethasone in Hospitalized Patients with Covid-19, N. Engl. J. Med. 384 (2021) 693–704. https://doi.org/10.1056/NEJMoa2021436.
[19] S. Whirledge, J.A. Cidlowski, Glucocorticoids, Stress, and Fertility, Minerva Endocrinol. 35 (2010) 109–125. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3547681/ (accessed April 3, 2021).
[20] M.Z. Tay, C.M. Poh, L. Rénia, P.A. MacAry, L.F.P. Ng, The trinity of COVID-19: immunity, inflammation and intervention, Nat. Rev. Immunol. 20 (2020) 363–374. https://doi.org/10.1038/s41577-020-0311-8.
[21] M. Gacci, M. Coppi, E. Baldi, A. Sebastianelli, C. Zaccaro, S. Morselli, A. Pecoraro, A. Manera, R. Nicoletti, A. Liaci, C. Bisegna, L. Gemma, S. Giancane, S. Pollini, A. Antonelli, F. Lagi, S. Marchiani, S. Dabizzi, S. Degl'Innocenti, F. Annunziato, M. Maggi, L. Vignozzi, A. Bartoloni, G.M. Rossolini, S. Serni, Semen impairment and occurrence of SARS-CoV-2 virus in semen after recovery from COVID-19, Hum. Reprod. Oxf. Engl. 36 (2021) 1520–1529. https://doi.org/10.1093/humrep/deab026.
[22] H. Li, X. Xiao, J. Zhang, M.I. Zafar, C. Wu, Y. Long, W. Lu, F. Pan, T. Meng, K. Zhao, L. Zhou, S. Shen, L. Liu, Q. Liu, C. Xiong, Impaired spermatogenesis in COVID-19 patients, EClinicalMedicine. 28 (2020) 100604. https://doi.org/10.1016/j.eclinm.2020.100604.
[23] A. Flaifel, M. Guzzetta, M. Occidental, B.B. Najari, J. Melamed, K.M. Thomas, F.-M. Deng, Testicular Changes Associated With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), Arch. Pathol. Lab. Med. 145 (2021) 8–9. https://doi.org/10.5858/arpa.2020-0487-LE.
[24] N. Asadi, M. Bahmani, A. Kheradmand, M. Rafieian-Kopaei, The Impact of Oxidative Stress on Testicular Function and the Role of Antioxidants in Improving it: A Review, J. Clin. Diagn. Res. JCDR. 11 (2017) IE01–IE05. https://doi.org/10.7860/JCDR/2017/23927.9886.
[25] R.J. Aitken, S.D. Roman, Antioxidant systems and oxidative stress in the testes, Oxid. Med. Cell. Longev. 1 (2008) 15–24. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2715191/ (accessed April 3, 2021).
[26] N. Moghimi, B. Eslami Farsani, M. Ghadipasha, G.-R. Mahmoudiasl, A. Piryaei, A. Aliaghaei, S. Abdi, H.-A. Abbaszadeh, M.-A. Abdollahifar, M. Forozesh, COVID-19 disrupts spermatogenesis through the oxidative stress pathway following induction of apoptosis, Apoptosis Int. J. Program. Cell Death. 26 (2021) 415–430. https://doi.org/10.1007/s10495-021-01680-2.
[27] D.P. Patel, N. Punjani, J. Guo, J.P. Alukal, P.S. Li, J.M. Hotaling, The impact of SARS-CoV-2 and COVID-19 on male reproduction and men's health, Fertil. Steril. 115 (2021) 813–823. https://doi.org/10.1016/j.fertnstert.2020.12.033.

[28] M. Hoffmann, H. Kleine-Weber, S. Schroeder, N. Krüger, T. Herrler, S. Erichsen, T.S. Schiergens, G. Herrler, N.-H. Wu, A. Nitsche, M.A. Müller, C. Drosten, S. Pöhlmann, SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor, Cell. 181 (2020) 271-280.e8. https://doi.org/10.1016/j.cell.2020.02.052.
[29] A.B. Reis, F.C. Araújo, V.M. Pereira, A.M. Dos Reis, R.A. Santos, F.M. Reis, Angiotensin (1-7) and its receptor Mas are expressed in the human testis: implications for male infertility, J. Mol. Histol. 41 (2010) 75–80. https://doi.org/10.1007/s10735-010-9264-8.
[30] K.E. Stanley, E. Thomas, M. Leaver, D. Wells, Coronavirus disease-19 and fertility: viral host entry protein expression in male and female reproductive tissues, Fertil. Steril. 114 (2020) 33–43. https://doi.org/10.1016/j.fertnstert.2020.05.001.
[31] F. Pan, X. Xiao, J. Guo, Y. Song, H. Li, D.P. Patel, A.M. Spivak, J.P. Alukal, X. Zhang, C. Xiong, P.S. Li, J.M. Hotaling, No evidence of severe acute respiratory syndrome–coronavirus 2 in semen of males recovering from coronavirus disease 2019, Fertil. Steril. 113 (2020) 1135–1139. https://doi.org/10.1016/j.fertnstert.2020.04.024.
[32] X. Ma, C. Guan, R. Chen, Y. Wang, S. Feng, R. Wang, G. Qu, S. Zhao, F. Wang, X. Wang, D. Zhang, L. Liu, A. Liao, S. Yuan, Pathological and molecular examinations of postmortem testis biopsies reveal SARS-CoV-2 infection in the testis and spermatogenesis damage in COVID-19 patients, Cell. Mol. Immunol. 18 (2021) 487–489. https://doi.org/10.1038/s41423-020-00604-5.
[33] J.D. Breidenbach, P. Dube, S. Ghosh, B.N. Abdullah, N.N. Modyanov, D. Malhotra, L.D. Dworkin, S.T. Haller, D.J. Kennedy, Impact of Comorbidities on SARS-CoV-2 Viral Entry-Related Genes, J. Pers. Med. 10 (2020). https://doi.org/10.3390/jpm10040146.
[34] C. Song, Y. Wang, W. Li, B. Hu, G. Chen, P. Xia, W. Wang, C. Li, F. Diao, Z. Hu, X. Yang, B. Yao, Y. Liu, Absence of 2019 Novel Coronavirus in Semen and Testes of COVID-19 Patients, Biol. Reprod. (2020). https://doi.org/10.1093/biolre/ioaa050.
[35] M. Hezavehei, B. Shokoohian, M.H. Nasr-Esfahani, A. Shpichka, P. Timashev, A. Shahverdi, M. Vosough, Possible Male Reproduction Complications after Coronavirus Pandemic, Cell J. Yakhteh. 23 (2021) 382–388. https://doi.org/10.22074/cellj.2021.7982.
[36] Pathological Findings in the Testes of COVID-19 Patients: Clinical Implications - European Urology Focus, (n.d.). https://www.eu-focus.europeanurology.com/article/S2405-4569(20)30144-9/fulltext (accessed April 3, 2021).
[37] Pathological and molecular examinations of postmortem testis biopsies reveal SARS-CoV-2 infection in the testis and spermatogenesis damage in COVID-19 patients | Cellular & Molecular Immunology, (n.d.). https://www.nature.com/articles/s41423-020-00604-5 (accessed April 3, 2021).
[38] J.K. Achua, K.Y. Chu, E. Ibrahim, K. Khodamoradi, K.S. Delma, O.A. Iakymenko, O.N. Kryvenko, H. Arora, R. Ramasamy, Histopathology and Ultrastructural Findings of Fatal COVID-19 Infections on Testis, World J. Mens Health. 39 (2021) 65–74. https://doi.org/10.5534/wjmh.200170.
[39] H. Alkhatatbeh, D. Alzaghari, A. Alkhashman, M. Azab, G.M.A. Edwan, M. Abufaraj, Does severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) cause orchitis in patients with coronavirus disease 2019 (COVID-19)?, Arab J. Urol. 18 (n.d.) 129–133. https://doi.org/10.1080/2090598X.2020.1798862.
[40] L. Chen, X. Huang, Z. Yi, Q. Deng, N. Jiang, C. Feng, Q. Zhou, B. Sun, W. Chen, R. Guo, Ultrasound Imaging Findings of Acute Testicular Infection in Patients With Coronavirus

Disease 2019: A Single-Center-Based Study in Wuhan, China, J. Ultrasound Med. Off. J. Am. Inst. Ultrasound Med. 40 (2021) 1787–1794. https://doi.org/10.1002/jum.15558.
[41] H. Feldmann, Virus in Semen and the Risk of Sexual Transmission, N. Engl. J. Med. 378 (2018) 1440–1441. https://doi.org/10.1056/NEJMe1803212.
[42] Y. Ruan, B. Hu, Z. Liu, K. Liu, H. Jiang, H. Li, R. Li, Y. Luan, X. Liu, G. Yu, S. Xu, X. Yuan, S. Wang, W. Yang, Z. Ye, J. Liu, T. Wang, No detection of SARS-CoV-2 from urine, expressed prostatic secretions, and semen in 74 recovered COVID-19 male patients: A perspective and urogenital evaluation, Andrology. 9 (2021) 99–106. https://doi.org/10.1111/andr.12939.
[43] B. Hajizadeh Maleki, B. Tartibian, COVID-19 and male reproductive function: a prospective, longitudinal cohort study, Reprod. Camb. Engl. 161 (2021) 319–331. https://doi.org/10.1530/REP-20-0382.
[44] N. Holtmann, P. Edimiris, M. Andree, C. Doehmen, D. Baston-Buest, O. Adams, J.-S. Kruessel, A.P. Bielfeld, Assessment of SARS-CoV-2 in human semen—a cohort study, Fertil. Steril. 114 (2020) 233–238. https://doi.org/10.1016/j.fertnstert.2020.05.028.
[45] M.Z. Temiz, M.M. Dincer, I. Hacibey, R.O. Yazar, C. Celik, S.H. Kucuk, G. Alkurt, L. Doganay, E. Yuruk, A.Y. Muslumanoglu, Investigation of SARS-CoV-2 in semen samples and the effects of COVID-19 on male sexual health by using semen analysis and serum male hormone profile: A cross-sectional, pilot study, Andrologia. 53 (2021) e13912. https://doi.org/10.1111/and.13912.
[46] D. Paoli, F. Pallotti, S. Colangelo, F. Basilico, L. Mazzuti, O. Turriziani, G. Antonelli, A. Lenzi, F. Lombardo, Study of SARS-CoV-2 in semen and urine samples of a volunteer with positive naso-pharyngeal swab, J. Endocrinol. Invest. 43 (2020) 1819–1822. https://doi.org/10.1007/s40618-020-01261-1.
[47] S.A. Rawlings, C. Ignacio, M. Porrachia, P. Du, D.M. Smith, A. Chaillon, No Evidence of SARS-CoV-2 Seminal Shedding Despite SARS-CoV-2 Persistence in the Upper Respiratory Tract, Open Forum Infect. Dis. 7 (2020) ofaa325. https://doi.org/10.1093/ofid/ofaa325.
[48] C. Pavone, G.M. Giammanco, D. Baiamonte, M. Pinelli, C. Bonura, M. Montalbano, G. Profeta, L. Curcurù, F. Bonura, Italian males recovering from mild COVID-19 show no evidence of SARS-CoV-2 in semen despite prolonged nasopharyngeal swab positivity, Int. J. Impot. Res. 32 (2020) 560–562. https://doi.org/10.1038/s41443-020-00344-0.
[49] B. Kayaaslan, G. Korukluoglu, I. Hasanoglu, A.K. Kalem, F. Eser, E. Akinci, R. Guner, Investigation of SARS-CoV-2 in Semen of Patients in the Acute Stage of COVID-19 Infection, Urol. Int. 104 (2020) 678–683. https://doi.org/10.1159/000510531.
[50] D. Li, M. Jin, P. Bao, W. Zhao, S. Zhang, Clinical Characteristics and Results of Semen Tests Among Men With Coronavirus Disease 2019, JAMA Netw. Open. 3 (2020). https://doi.org/10.1001/jamanetworkopen.2020.8292.
[51] SART and ASRM Issue Advice for Infertility Patients Concerning the Novel Coronavirus (COVID-19), (n.d.). https://www.asrm.org/news-and-publications/news-and-research/press-releases-and-bulletins/sart-and-asrm-issue-advice-for-infertility-patients-concerning-the-novel-coronavirus-covid-19/ (accessed April 7, 2021).
[52] M.É. Czeisler, Delay or Avoidance of Medical Care Because of COVID-19–Related Concerns — United States, June 2020, MMWR Morb. Mortal. Wkly. Rep. 69 (2020). https://doi.org/10.15585/mmwr.mm6936a4.

[53] S.C. Esteves, F. Lombardo, N. Garrido, J. Alvarez, A. Zini, G.M. Colpi, J. Kirkman-Brown, S.E.M. Lewis, L. Björndahl, A. Majzoub, C.-L. Cho, P. Vendeira, J. Hallak, E. Amar, M. Cocuzza, F.C. Bento, R.C. Figueira, R. Sciorio, R.J. Laursen, A.M. Metwalley, S.K. Jindal, S. Parekattil, R. Ramasamy, C. Alviggi, P. Humaidan, J.L. Yovich, A. Agarwal, SARS-CoV-2 pandemic and repercussions for male infertility patients: A proposal for the individualized provision of andrological services, Andrology. 9 (2021) 10–18. https://doi.org/10.1111/andr.12809.

[54] A. Ahmad, M. Zaheer, F.J. Balis, Baricitinib, in: StatPearls, StatPearls Publishing, Treasure Island (FL), 2021. http://www.ncbi.nlm.nih.gov/books/NBK572064/ (accessed October 15, 2021).

[55] L. Pascolo, G. Zito, L. Zupin, S. Luppi, E. Giolo, M. Martinelli, D. De Rocco, S. Crovella, G. Ricci, Renin Angiotensin System, COVID-19 and Male Fertility: Any Risk for Conceiving?, Microorganisms. 8 (2020) 1492. https://doi.org/10.3390/microorganisms8101492.

[56] K. Narayana, U.J.A. D'Souza, P. Narayan, G. Kumar, The antiviral drug ribavirin reversibly affects the reproductive parameters in the male Wistar rat, Folia Morphol. 64 (2005) 65–71.

[57] J.W. Millsop, M.M. Heller, M.J. Eliason, J.E. Murase, Dermatological medication effects on male fertility, Dermatol. Ther. 26 (2013) 337–346. https://doi.org/10.1111/dth.12069.

[58] E.Z. Drobnis, A.K. Nangia, Antivirals and Male Reproduction, Adv. Exp. Med. Biol. 1034 (2017) 163–178. https://doi.org/10.1007/978-3-319-69535-8_11.

[59] D. Gore, Posts Spread Dubious Claim About Ivermectin and Male Fertility, FactCheck.Org. (2021). https://www.factcheck.org/2021/09/posts-spread-dubious-claim-about-ivermectin-and-male-fertility/ (accessed November 25, 2021).

[60] Scholars Research Library | Effects of Ivermectin therapy on the sperm functions of Nigerian onchocerciasis patients |, (n.d.). https://www.scholarsresearchlibrary.com/search-results.php?keyword=Effects+of+Ivermectin+therapy+on+the+sperm+functions+of+Nigerian+onchocerciasis+patients (accessed November 25, 2021).

[61] Z.K. El-Maddawy, W.S.H. Abd El Naby, Effects of ivermectin and its combination with alpha lipoic acid on expression of IGFBP-3 and HSPA1 genes and male rat fertility, Andrologia. 50 (2018). https://doi.org/10.1111/and.12891.

[62] J.C. Best, M. Kuchakulla, K. Khodamoradi, T.F.N. Lima, F.S. Frech, J. Achua, O. Rosete, B. Mora, H. Arora, E. Ibrahim, R. Ramasamy, Evaluation of SARS-CoV-2 in Human Semen and Effect on Total Sperm Number: A Prospective Observational Study, World J. Mens Health. 39 (2021) 489–495. https://doi.org/10.5534/wjmh.200192.

[63] S.A. Meo, I.A. Bukhari, J. Akram, A.S. Meo, D.C. Klonoff, COVID-19 vaccines: comparison of biological, pharmacological characteristics and adverse effects of Pfizer/BioNTech and Moderna Vaccines, Eur. Rev. Med. Pharmacol. Sci. 25 (2021) 1663–1669. https://doi.org/10.26355/eurrev_202102_24877.

[64] E.H. Livingston, P.N. Malani, C.B. Creech, The Johnson & Johnson Vaccine for COVID-19, JAMA. (2021). https://doi.org/10.1001/jama.2021.2927.

[65] D.C. Gonzalez, D.E. Nassau, K. Khodamoradi, E. Ibrahim, R. Blachman-Braun, J. Ory, R. Ramasamy, Sperm Parameters Before and After COVID-19 mRNA Vaccination, JAMA. 326 (2021) 273–274. https://doi.org/10.1001/jama.2021.9976.